Public Assessment Report

Decentralised Procedure

AMLODIPINE 5 MG AND 10 MG TABLETS

AMLODIPINE BESILATE

UK/H/0862/001-2/DC

ARROW GENERICS LIMITED
LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Arrow Generics Limited Marketing Authorisations (licences) for the medicinal products Amlodipine 5 mg and 10 mg Tablets (Product Licence numbers: 18909/0173-4). These medicines are available on prescription only.

Amlodipine 5 mg and 10 mg Tablets treat high blood pressure (hypertension) by relaxing the blood vessels so that blood passes through them more easily. These tablets are also used in the treatment of a type of chest pain known as angina. Angina occurs when not enough blood reaches the heart and amlodipine helps prevent this by increasing the blood supply to the heart.

The data submitted in support of the application for Amlodipine 5 mg and 10 mg Tablets raised no clinically significant safety concerns and it was therefore judged that the benefits of using this product outweigh the risks; hence a Marketing Authorisation has been granted.
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## Module 1

| **Product Name** | Amlodipine 5 mg Tablets  
Amlodipine 10 mg Tablets |
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<tr>
<td><strong>Type of Application</strong></td>
<td>Generic application, Article 10(1)</td>
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<td><strong>Active Substance</strong></td>
<td>Amlodipine besilate</td>
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<td><strong>Pharmaceutical form and strength(s)</strong></td>
<td>Tablet, 6.94 mg or 13.88 mg amlodipine besilate/tablet (equivalent to 5 or 10 mg amlodipine base/tablet)</td>
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</table>
| **Procedure Numbers** | UK/H/0862/001/DC  
UK/H/0862/002/DC |
| **Reference Member State (RMS)** | United Kingdom (UK) |
| **Concerned Member States (CMS)** | Belgium (BE), The Czech Republic (CZ), Germany (DE), Denmark (DK), Hungary (HU), Italy (IT), Malta (MT), the Netherlands (NL), Norway (NO), Poland (PL), Portugal (PT), Sweden (SE), Slovenia (SI), The Slovak Republic (SK) |
| **Date of start of the procedure** | 7 April 2006 |
| **End date of decentralised procedure** | 7 March 2007 |
| **Marketing Authorisation Number(s)** | PL 18909/0173  
PL 18909/0174 |
| **Name and address of the authorisation holder** | Arrow Generics Ltd  
Unit 2, Eastman Way  
Stevenage, Hertfordshire  
SG1 4SZ, United Kingdom |
Module 2
Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Amlodipine 5 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 5 mg of amlodipine (as amlodipine besilate).
For a full list of excipients see Section 6.1.

3 PHARMACEUTICAL FORM
Tablet.
White to off-white, elongated octagon-shaped tablets, embossed with ‘AM 5’ on one side and ‘>’ on the other side.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Essential hypertension.
Chronic stable and vasospastic angina pectoris.

4.2 Posology and method of administration
In adults
For treatment of both hypertension and angina pectoris the usual initial dose is 5 mg once daily. If the desired therapeutic effect cannot be achieved within 2-4 weeks, this dose may be increased to a maximum dose of 10 mg daily (as single dose) depending on the individual patient’s response. Amlodipine may be used either as monotherapy or in combination with other antianginal drugs in patients with angina.

In children and adolescents (less than 18 years of age)
Amlodipine is not recommended in children and adolescents due to insufficient data on safety and efficacy.

In the elderly
Normal dosage regimens are recommended in the elderly, but caution should be exercised when increasing the dosage (see section 5.2).

In patients with renal impairment
In these patients amlodipine can be used in the normal dosage (see section 5.2). Amlodipine is not dialyzable.

In patients with hepatic impairment
A dosage regimen for patients with hepatic impairment has not been established, therefore amlodipine should be administered with caution (see section 4.4).

The tablets should be taken with a glass of water independently from meals.

4.3 Contraindications
Amlodipine is contra-indicated in patients with:
- hypersensitivity to amlodipine, dihydropyridine derivatives or to any of the excipients
- severe hypotension
- shock, including cardiogenic shock
- heart failure after acute myocardial infarction (during the first 28 days)
- obstruction of the outflow tract of the left ventricle (e.g. high grade aortic stenosis)
- unstable angina pectoris

4.4 Special warnings and precautions for use
There are no data to support the use of amlodipine alone, during or within one month of myocardial infarction. The safety and efficacy of amlodipine in hypertensive crisis has not been established.

Amlodipine should be administered with caution to patients with low cardiac reserve.
Patients with heart failure

Patients with cardiac failure should be treated with caution. In a long-term study including patients suffering from severe heart failure (NYHA grade III and IV) the reported incidence of pulmonary oedema was higher in the amlodipine treated group than in the placebo group, but this was not indicating an aggravation of the heart failure (see Section 5.1).

Use in patients with impaired hepatic function

The half-life of amlodipine is prolonged in patients with impaired liver function; dosage recommendations have not been established. Amlodipine should therefore be administered with caution in these patients.

Use in elderly patients

In the elderly, increase of the dosage should take place with care (see Section 5.2).

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on amlodipine

CYP3A4 inhibitors: A study of elderly patients has shown that diltiazem inhibits metabolism of amlodipine, probably via CYP3A4, since plasma concentration increases by approx. 50% and the effect of amlodipine is increased. It cannot be excluded that stronger inhibitors of CYP3A4 (i.e. ketoconazole, itraconazole, ritonavir) increase the plasma concentration of amlodipine to a greater extent than diltiazem. Caution should be exercised in combination of amlodipine and CYP3A4 inhibitors.

CYP3A4 inducers: There is no information available on the effect of CYP3A4 inducers (i.e. rifampicin, St. John's wort) on amlodipine. Co-administration may lead to reduced plasma concentration of amlodipine. Caution should be exercised in combination of amlodipine and CYP3A4 inducers.

In clinical interaction studies grapefruit juice, cimetidine, aluminium/magnesium (antacid) and sildenafil did not affect the pharmacokinetics of amlodipine.

Effects of amlodipine on other medicinal products

Amlodipine may potentiate the effect of other antihypertensive agents, such as beta-adrenoceptor blocking agents, ACE-inhibitors, alpha-1-blockers and diuretics. In patients with an increased risk (for example after myocardial infarction) the combination of a calcium channel blocker with a beta-adrenoceptor blocking agent may lead to heart failure, to hypotension and to a (new) myocardial infarction.

In clinical interaction studies, amlodipine did not affect the pharmacokinetics of atorvastatin, digoxin, warfarin or ciclosporin.

There is no effect of amlodipine on laboratory parameters.

4.6 Pregnancy and lactation

There are no adequate data from the use of amlodipine in pregnant women.

In animal studies effects on reproduction were found at high dosages (see section 5.3). The potential risk for humans is unknown. Accordingly amlodipine should not be used during pregnancy unless clearly needed.

It is not known whether amlodipine is excreted in breast milk. It is advised to stop breastfeeding during treatment with amlodipine.

4.7 Effects on ability to drive and use machines

In patients suffering from dizziness, headache, fatigue or nausea the ability to react may be impaired.

4.8 Undesirable effects

The following convention has been utilised for the classification of undesirable effects:

Very common: >1/10
Common: >1/100 and <1/10
Uncommon: >1/1000 and <1/100
PAR Amlodipine 5 mg and 10 mg Tablets

Rare: >1/10 000 and <1/1000
Very rare: <1/10 000
Not known: Cannot be established from the available data

Blood and lymphatic system disorders:
Very rare: Leukocytopenia, thrombocytopenia.

Endocrine disorders:
Uncommon: Gynaecomastia.

Metabolism and nutrition disorders:
Very rare: Hyperglycaemia.

Nervous system disorders:
Common: Headache (especially at the beginning of the treatment), Fatigue, dizziness, asthenia
Uncommon: Malaise, dry mouth, tremor, paraesthesia, increased sweating
Rare: Taste changes
Very rare: Peripheral neuropathy

Eye disorders:

Psychiatric disorders:
Uncommon: Sleep disorder, irritability, depression
Rare: Confusion, mood changes including anxiety.

Ear and labyrinth disorders:
Rare: Tinnitus

Cardiac disorders:
Common: Palpitations
Uncommon: Syncope, tachycardia, chest pain, at the beginning of treatment aggravation of angina pectoris may happen, isolated cases of myocardial infarction and arrhythmias (including extrasystole, ventricular tachycardia, bradycardia and atrial arrhythmias) and chest pain have been reported in patients with coronary artery disease, but a clear association with amlodipine has not been established

Vascular disorders:
Uncommon: Hypotension
Very rare: Vasculitis.

Respiratory, thoracic and mediastinal disorders:
Uncommon: Dyspnoea, Rhinitis
Very rare: Cough.

Gastrointestinal disorders:
Common: Nausea, dyspepsia, abdominal pain
Uncommon: Vomiting, diarrhoea, constipation, gingival hyperplasia
Very rare: Gastritis.

Hepato-biliary disorders:
Rare: Elevated liver enzymes, jaundice, hepatitis
Very rare: Pancreatitis

Skin and subcutaneous tissue disorders:
Very common: Ankle swelling
Common: Facial flushing with heat sensation, especially at the beginning of the treatment
Uncommon: Exanthema, pruritus, urticaria, alopecia, skin discolouration
Very rare: Angioedema, isolated cases of allergic reactions including pruritus, rash, angioedema and erythema exsudativum multiforme, exfoliative dermatitis and Stevens Johnson syndrome and Quincke oedema have been reported.

Musculoskeletal, connective tissue and bone disorders:
Uncommon: Muscle cramps, back pain, myalgia and arthralgia.

Renal and urinary disorders:
Uncommon: Increased micturition frequency.

Reproductive system and breast disorders:
Uncommon: Impotence.

General disorders and administration site conditions:
Uncommon: Increase or decrease of weight.

4.9 Overdose
In humans, experience with intentional overdose is limited. Available data suggest that overdose (>100 mg) could result in excessive peripheral vasodilatation with subsequent marked and probably prolonged systemic hypotension.

Clinically significant hypotension due to amlodipine overdose calls for active cardiovascular support including frequent monitoring of cardiac and respiratory function, elevation of extremities, and attention to circulating fluid volume and urine output.

A vasoconstrictor may be helpful in restoring vascular tone and blood pressure, provided that there is no contraindication to its use. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade. Gastric lavage may be worthwhile in some cases. In healthy volunteers the use of charcoal up to 2h after administration of amlodipine 10mg has been shown to reduce the absorption rate of amlodipine. Since amlodipine is highly protein-bound, dialysis is not likely to be of benefit.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Dihydropyridine derivatives
ATC code: C08C A01

Amlodipine is a calcium antagonist and inhibits the influx of calcium ions into cardiac and vascular smooth muscle cells. The mechanism of the antihypertensive action is due to the direct relaxant effect on vascular smooth muscle cells. The precise mechanism by which amlodipine relieves angina pectoris has not been fully determined, but the following two actions play a role:

1. Amlodipine dilates peripheral arterioles and thus reduces the total peripheral resistance (afterload) against which the heart pumps. This unloading of the heart reduces myocardial energy consumption and oxygen requirements.

2. Dilatation of the main coronary arteries and the coronary arterioles also probably plays a role in its action. This dilation increases the supply in oxygen to myocardiac muscle in patients with Prinzmetal anginal attack.

In patients with hypertension, once daily dosing provides clinically significant reductions of blood pressure (in both supine and standing positions) that persist for 24 hours.

In patients with angina pectoris, once daily administration of amlodipine increases total exercise time, the delay of occurrence of anginal attack and the delay of the occurrence of a 1-mm ST interval. Amlodipine decreases both attack frequency and glyceryl trinitrate tablet consumption.

In haemodynamic studies in patients with heart failure and in clinical studies based on exercise tests in patients with NYHA class II-IV heart failure, amlodipine was found not to cause any clinical deterioration, as measured by exercise tolerance, left ventricular ejection fraction and clinical signs and symptoms.
In a placebo-controlled study (PRAISE) designed to evaluate patients with NYHA class III-IV heart failure treated with digoxin, diuretics and ACE inhibitors, amlodipine was shown not to cause any increase in the risk of death or in the combined risk of mortality and morbidity in patients with heart failure.

A follow-up study (PRAISE 2) showed that amlodipine did not have an effect on the total or cardiovascular mortality in class III-IV heart failure patients without ischaemic origin. In this study treatment with amlodipine was associated with an increase in pulmonary oedema, although this could not be related to an increase in symptoms.

5.2 Pharmacokinetic properties

Absorption/Distribution
After oral administration of therapeutic doses amlodipine is slowly absorbed from the gastrointestinal tract. The absorption of amlodipine is unaffected by the concomitant intake of food. The absolute bioavailability of the active substance is estimated as 64-80%. Peak plasma levels are reached 6 to 12 hours post-dose. The volume of distribution is about 20 l/kg. The pKa of amlodipine is 8.6. Plasma protein binding in vitro is approximately 98%.

Metabolism/Elimination
The plasma elimination half-life is about 35 to 50 hours.

Steady state plasma levels are reached after 7-8 consecutive days.

Amlodipine is extensively metabolised to inactive metabolites. About 60% of the administered dose is excreted in the urine, about 10% of which in the form of unchanged amlodipine.

In the elderly
The time to reach peak plasma concentrations is the same in elderly and younger patients. Clearance may be reduced in elderly patients so that the area under the curve (AUC) and the terminal elimination half-life are increased. The recommended dosage regimen for elderly patients is however the same, although caution should be exercised when increasing the dosage.

In patients with impaired renal function
Amlodipine is extensively biotransformed to inactive metabolites. Ten percent of the substance is excreted unchanged in the urine. Changes in amlodipine plasma concentration are not correlated with the degree of renal impairment. In these patients amlodipine may be administered at the normal dosage. Amlodipine is not dialysable.

Patients with hepatic impairment:
The half-life of amlodipine is prolonged in patients with impaired hepatic function.

5.3 Preclinical safety data
Preclinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicity, genotoxicity and carcinogenic potential. In reproductive toxicity studies in rats at high doses, delayed parturition, difficult labour and reduced foetal and pup survival were seen.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Calcium hydrogen phosphate dihydrate
Microcrystalline cellulose
Sodium starch glycolate (type A)
Magnesium stearate

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years.
6.4 Special precautions for storage
Store below 25°C.

6.5 Nature and contents of container
PVC/Aclar/Aluminium Foil Blister Packs.
*Pack sizes 10, 20, 28, 30, 50, 56, 60, 98, 100, 300 tablets.
* Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Arrow Generics Limited
Unit 2, Eastman Way
Stevenage
Hertfordshire
SG1 4SZ
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 18909/0173

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
07/03/2007

10 DATE OF REVISION OF THE TEXT
07/03/2007
1 NAME OF THE MEDICINAL PRODUCT
Amlodipine 10 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 10 mg of amlodipine (as amlodipine besilate).
For a full list of excipients see Section 6.1.

3 PHARMACEUTICAL FORM
Tablet.
White to off-white, elongated octagon-shaped tablets, embossed with ‘AM 10’ on one side and ‘>’ on the other side.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Essential hypertension.
Chronic stable and vasospastic angina pectoris.

4.2 Posology and method of administration
In adults
For treatment of both hypertension and angina pectoris the usual initial dose is 5 mg once daily. If the desired therapeutic effect cannot be achieved within 2-4 weeks, this dose may be increased to a maximum dose of 10 mg daily (as single dose) depending on the individual patient’s response. Amlodipine may be used either as monotherapy or in combination with other antianginal drugs in patients with angina.

In children and adolescents (less than 18 years of age)
Amlodipine is not recommended in children and adolescents due to insufficient data on safety and efficacy.

In the elderly
Normal dosage regimens are recommended in the elderly, but caution should be exercised when increasing the dosage (see section 5.2).

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In these patients amlodipine can be used in the normal dosage (see section 5.2). Amlodipine is not dialyzable.

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A dosage regimen for patients with hepatic impairment has not been established, therefore amlodipine should be administered with caution (see section 4.4).

The tablets should be taken with a glass of water independently from meals.

4.3 Contraindications
Amlodipine is contra-indicated in patients with:
- hypersensitivity to amlodipine, dihydropyridine derivatives or to any of the excipients
- severe hypotension
- shock, including cardiogenic shock
- heart failure after acute myocardial infarction (during the first 28 days)
- obstruction of the outflow tract of the left ventricle (e.g. high grade aortic stenosis)
- unstable angina pectoris

4.4 Special warnings and precautions for use
There are no data to support the use of amlodipine alone, during or within one month of myocardial infarction. The safety and efficacy of amlodipine in hypertensive crisis has not been established.

Amlodipine should be administered with caution to patients with low cardiac reserve.
Patients with heart failure
Patients with cardiac failure should be treated with caution. In a long-term study including patients suffering from severe heart failure (NYHA grade III and IV) the reported incidence of pulmonary oedema was higher in the amlodipine treated group than in the placebo group, but this was not indicating an aggravation of the heart failure (see Section 5.1).

Use in patients with impaired hepatic function
The half-life of amlodipine is prolonged in patients with impaired liver function; dosage recommendations have not been established. Amlodipine should therefore be administered with caution in these patients.

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CYP3A4 inducers: There is no information available on the effect of CYP3A4 inducers (i.e. rifampicin, St. John's Wort) on amlodipine. Co-administration may lead to reduced plasma concentration of amlodipine. Caution should be exercised in combination of amlodipine and CYP3A4 inducers.

In clinical interaction studies grapefruit juice, cimetidine, aluminium/magnesium (antacid) and sildenafil did not affect the pharmacokinetics of amlodipine.

Effects of amlodipine on other medicinal products
Amlodipine may potentiate the effect of other antihypertensive agents, such as beta-adrenoceptor blocking agents, ACE-inhibitors, alpha-1-blockers and diuretics. In patients with an increased risk (for example after myocardial infarction) the combination of a calcium channel blocker with a beta-adrenoceptor blocking agent may lead to heart failure, to hypotension and to a (new) myocardial infarction.

In clinical interaction studies, amlodipine did not affect the pharmacokinetics of atorvastatin, digoxin, warfarin or ciclosporin.

There is no effect of amlodipine on laboratory parameters.

4.6 Pregnancy and lactation
There are no adequate data from the use of amlodipine in pregnant women.

In animal studies effects on reproduction were found at high dosages (see section 5.3). The potential risk for humans is unknown. Accordingly amlodipine should not be used during pregnancy unless clearly needed.

It is not known whether amlodipine is excreted in breast milk. It is advised to stop breastfeeding during treatment with amlodipine.

4.7 Effects on ability to drive and use machines
In patients suffering from dizziness, headache, fatigue or nausea the ability to react may be impaired.

4.8 Undesirable effects
The following convention has been utilised for the classification of undesirable effects:

Very common: >1/10
Common: >1/100 and <1/10
Uncommon: >1/1000 and <1/100
Rare: >1/10 000 and <1/1000
Very rare: <1/10 000
Not known: Cannot be established from the available data.

Blood and lymphatic system disorders:
Very rare: Leukocytopenia, thrombocytopenia.

Endocrine disorders:
Uncommon: Gynaecomastia.

Metabolism and nutrition disorders:
Very rare: Hyperglycaemia.

Nervous system disorders:
Common: Headache (especially at the beginning of the treatment), Fatigue, dizziness, asthenia
Uncommon: Malaise, dry mouth, tremor, paraesthesia, increased sweating
Rare: Taste changes
Very rare: Peripheral neuropathy

Eye disorders:

Psychiatric disorders:
Uncommon: Sleep disorder, irritability, depression
Rare: Confusion, mood changes including anxiety.

Ear and labyrinth disorders:
Rare: Tinnitus

Cardiac disorders:
Common: Palpitations
Uncommon: Syncope, tachycardia, chest pain, at the beginning of treatment aggravation of angina pectoris may happen, isolated cases of myocardial infarction and arrhythmias (including extrasystole, ventricular tachycardia, bradycardia and atrial arrhythmias) and chest pain have been reported in patients with coronary artery disease, but a clear association with amlodipine has not been established

Vascular disorders:
Uncommon: Hypotension
Very rare: Vasculitis.

Respiratory, thoracic and mediastinal disorders:
Uncommon: Dyspnoea, Rhinitis
Very rare: Cough.

Gastrointestinal disorders:
Common: Nausea, dyspepsia, abdominal pain
Uncommon: Vomiting, diarrhoea, constipation, gingival hyperplasia
Very rare: Gastritis.

Hepato-biliary disorders:
Rare: Elevated liver enzymes, jaundice, hepatitis
Very rare: Pancreatitis

Skin and subcutaneous tissue disorders:
Very common: Ankle swelling
Common: Facial flushing with heat sensation, especially at the beginning of the treatment
Uncommon: Exanthema, pruritus, urticaria, alopecia, skin discolouration
Very rare: Angioedema, isolated cases of allergic reactions including pruritus, rash, angioedema and erythema exsudativum multiforme, exfoliative dermatitis and Stevens Johnson syndrome and Quincke oedema have been reported.
Musculoskeletal, connective tissue and bone disorders:
Uncommon: Muscle cramps, back pain, myalgia and arthralgia.

Renal and urinary disorders:
Uncommon: Increased micturition frequency.

Reproductive system and breast disorders:
Uncommon: Impotence.

General disorders and administration site conditions:
Uncommon: Increase or decrease of weight.

4.9 Overdose
In humans, experience with intentional overdose is limited. Available data suggest that overdose (>100 mg) could result in excessive peripheral vasodilatation with subsequent marked and probably prolonged systemic hypotension.

Clinically significant hypotension due to amlodipine overdose calls for active cardiovascular support including frequent monitoring of cardiac and respiratory function, elevation of extremities, and attention to circulating fluid volume and urine output.

A vasoconstrictor may be helpful in restoring vascular tone and blood pressure, provided that there is no contraindication to its use. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade. Gastric lavage may be worthwhile in some cases. In healthy volunteers the use of charcoal up to 2h after administration of amlodipine 10mg has been shown to reduce the absorption rate of amlodipine. Since amlodipine is highly protein-bound, dialysis is not likely to be of benefit.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Dihydropyridine derivatives
ATC code: C08C A01

Amlodipine is a calcium antagonist and inhibits the influx of calcium ions into cardiac and vascular smooth muscle cells. The mechanism of the antihypertensive action is due to the direct relaxant effect on vascular smooth muscle cells. The precise mechanism by which amlodipine relieves angina pectoris has not been fully determined, but the following two actions play a role:

1. Amlodipine dilates peripheral arterioles and thus reduces the total peripheral resistance (afterload) against which the heart pumps. This unloading of the heart reduces myocardial energy consumption and oxygen requirements.

2. Dilatation of the main coronary arteries and the coronary arterioles also probably plays a role in its action. This dilation increases the supply in oxygen to myocardiac muscle in patients with Prinzmetal anginal attack.

In patients with hypertension, once daily dosing provides clinically significant reductions of blood pressure (in both supine and standing positions) that persist for 24 hours.

In patients with angina pectoris, once daily administration of amlodipine increases total exercise time, the delay of occurrence of anginal attack and the delay of the occurrence of a 1-mm ST interval. Amlodipine decreases both attack frequency and glyceryl trinitrate tablet consumption.

In haemodynamic studies in patients with heart failure and in clinical studies based on exercise tests in patients with NYHA class II-IV heart failure, amlodipine was found not to cause any clinical deterioration, as measured by exercise tolerance, left ventricular ejection fraction and clinical signs and symptoms.

In a placebo-controlled study (PRAISE) designed to evaluate patients with NYHA class III-IV heart failure treated with digoxin, diuretics and ACE inhibitors, amlodipine was shown not to cause any increase in the risk of death or in the combined risk of mortality and morbidity in patients with heart failure.
A follow-up study (PRAISE 2) showed that amlodipine did not have an effect on the total or cardiovascular mortality in class III-IV heart failure patients without ischaemic origin. In this study treatment with amlodipine was associated with an increase in pulmonary oedema, although this could not be related to an increase in symptoms.

5.2 Pharmacokinetic properties

Absorption/Distribution
After oral administration of therapeutic doses amlodipine is slowly absorbed from the gastrointestinal tract. The absorption of amlodipine is unaffected by the concomitant intake of food. The absolute bioavailability of the active substance is estimated as 64-80%. Peak plasma levels are reached 6 to 12 hours post-dose. The volume of distribution is about 20 l/kg. The pKa of amlodipine is 8.6. Plasma protein binding in vitro is approximately 98%.

Metabolism/Elimination
The plasma elimination half-life is about 35 to 50 hours.

Steady state plasma levels are reached after 7-8 consecutive days.

Amlodipine is extensively metabolised to inactive metabolites. About 60% of the administered dose is excreted in the urine, about 10% of which in the form of unchanged amlodipine.

In the elderly
The time to reach peak plasma concentrations is the same in elderly and younger patients. Clearance may be reduced in elderly patients so that the area under the curve (AUC) and the terminal elimination half-life are increased. The recommended dosage regimen for elderly patients is however the same, although caution should be exercised when increasing the dosage.

In patients with impaired renal function
Amlodipine is extensively biotransformed to inactive metabolites. Ten percent of the substance is excreted unchanged in the urine. Changes in amlodipine plasma concentration are not correlated with the degree of renal impairment. In these patients amlodipine may be administered at the normal dosage. Amlodipine is not dialysable.

Patients with hepatic impairment:
The half-life of amlodipine is prolonged in patients with impaired hepatic function.

5.3 Preclinical safety data
Preclinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicity, genotoxicity and carcinogenic potential. In reproductive toxicity studies in rats at high doses, delayed parturition, difficult labour and reduced foetal and pup survival were seen.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Calcium hydrogen phosphate dihydrate
Microcrystalline cellulose
Sodium starch glycolate (type A)
Magnesium stearate

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years.

6.4 Special precautions for storage
Store below 25°C.

6.5 Nature and contents of container
PVC/Aclar/Aluminium Foil Blister Packs.
PAR Amlodipine 5 mg and 10 mg Tablets

*Pack sizes 10, 14, 20, 28, 30, 50, 56, 60, 98, 100 tablets.  
* Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Arrow Generics Limited
Unit 2, Eastman Way
Stevenage
Hertfordshire
SG1 4SZ
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 18909/0174

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
07/03/2007

10 DATE OF REVISION OF THE TEXT
07/03/2007
Module 3
Product Information Leaflets

Amlodipine 5 mg and 10 mg Tablets

Package Leaflet: Information for the User

Amlodipine 5 mg and 10 mg Tablets (Amlodipine besilate)

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Amlodipine Tablets are and what they are used for
2. Before you take Amlodipine Tablets
3. How to take Amlodipine Tablets
4. Possible side effects
5. How to store Amlodipine Tablets
6. Further information

1. WHAT AMLODIPINE TABLETS ARE AND WHAT THEY ARE USED FOR

Amlodipine Tablets are used to treat high blood pressure (hypertension) or a certain type of chest pain called angina, including Prinzmetal’s (or variant) angina. Amlodipine is one of a group of medicines called calcium channel blockers. If you have high blood pressure, amloidipine works by relaxing blood vessels, so that blood passes through them more easily. If you have angina, you may get chest pains when your heart cannot get enough blood. This usually happens during exercise or stress. Amlodipine helps to prevent this by increasing the blood supply to the heart. Amlodipine tablets do not work immediately to stop the chest pain from angina.

2. BEFORE YOU TAKE AMLODIPINE TABLETS

Do not take Amlodipine Tablets:
- If you are allergic (hypersensitive) to amlodipine, other calcium channel blockers or any of the other ingredients in the tablets (these are listed in section 6. Further Information).
- If you have had a heart attack within the last 28 days.
- If you are suffering from obstruction to the outflow of blood from the left main chamber of the heart.
- If you are suffering from unstable angina (angina at rest or at night).
- If you are suffering from very low blood pressure (severe hypotension).

Take special care with Amlodipine Tablets

Before you take Amlodipine Tablets tell your doctor:
- If you have any liver problems.
- If you have a history of blood in your stools (abnormal bowel movements).
- If you have had a heart attack.

If any of the above apply to you, talk to your doctor who will decide what to do.

Taking other medicines

Tell your doctor if you are taking or have taken any of the following medicines as they may interact with your Amlodipine tablets:
- Medicines called antifungal agents (such as ketoconazole or itraconazole), which are used to treat infections caused by fungi or yeasts, e.g. thrush and ringworm
- Medicines used to treat infections caused by viruses (antiviral agents), such as zidovudine used in the treatment of HIV infections
- Medicines used to treat infections caused by bacteria and yeasts (antibiotics), such as clindamycin used in the treatment of tuberculosis
- Herbal medicines used to treat depression such as St John’s Wort
- Dilatiazem, another medicine used to treat high blood pressure and angina
- Other medicines for the treatment of high blood pressure, e.g. ACE inhibitors such as enalapril or captopril, alpha-1-blockers such as doxazosin or tamsulosin, beta-blockers such as metoprolol or sotalol and diuretics (water tablets) such as furosemide or amiloride.

It may still be alright for you to take Amlodipine Tablets and your doctor will be able to decide what is suitable for you.

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Pregnancy and breast-feeding

There is very little information on whether it is harmful to take amlodipine during pregnancy. Amlodipine must only be used during pregnancy if your doctor decides that it is absolutely necessary. There is no information on the use of amlodipine while breast-feeding. You are advised not to breast-feed when using amloidipine.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

The tablets may make you feel dizzy, tired or nauseous. Therefore care is recommended when driving or using machines.

3. HOW TO TAKE AMLODIPINE TABLETS

Always take Amlodipine Tablets exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

The tablets will be told you how many tablets you should take and when. The tablets should be swallowed whole with plenty of water and not with your meals. Take your tablets at the same time each day.

Adults and the elderly

The usual dose of amlodipine is one tablet daily. Your doctor may start your treatment with Amlodipine 5 mg Tablets and increase your dosage to Amlodipine 10 mg Tablets depending on how you get on.

Amlodipine Tablets are not recommended for children or adolescents (under 18 years old).

If you take more Amlodipine Tablets than you should

If you have accidentally taken more than your prescribed dose, contact your nearest casualty department or tell your doctor or pharmacist immediately. Remember to take the tablet and any remaining tablets with you.

If you forget to take Amlodipine Tablets

If you forget to take a tablet, simply leave out that dose completely and then take your next dose at the right time. Do not take a double dose to make up for a forgotten dose.

If you have any further questions on the use of this product, ask your doctor or pharmacist.
4. POSSIBLE SIDE EFFECTS

Like all medicines, Amlodipine Tablets can cause side effects, although not everyone gets them.

All medicines can cause allergic reactions although serious allergic reactions are very rare. If you get any of the following symptoms after taking these tablets, contact your doctor immediately:
- any sudden wheeze, difficulty in breathing or dizziness, swelling of the eyelids, face, lips or throat
- peeling and blistering of the skin, mouth, eyes and genitals
- rash affecting your whole body.

The following side effects have also been reported:

Very common side effects (probably affecting more than 1 in 10 people)
- swelling of the ankles

Common side effects (probably affecting up to 1 in 10 people)
- headache
- feeling tired
- dizziness
- weakness
- feeling sick
- stomach ache
- indigestion
- flushing of the face
- palpitations (a quicker or irregular heart beat).

Uncommon side effects (probably affecting fewer than 1 in 100 people)
- feeling unwell
- dry mouth
- tremor (shaking)
- pins and needles
- increased sweating
- difficulty sleeping
- irritability
- depression
- shortness of breath
- rhinitis (runny nose)
- vomiting (being sick)
- diarrhoea or constipation
- swelling or soreness of the gums
- muscle cramps
- back pain
- muscle or joint pain
- increased need to urinate (pass water)
- change in your weight
- inability to obtain an erection
- fainting
- chest pains
- increased heart rate
- low blood pressure
- skin rash
- itching
- local swelling causing wheals on the skin (‘nettle rash’)
- hair loss
- discolouration of the skin
- visual disturbances
- enlargement of male breasts.

Rare side effects (probably affecting fewer than 1 in 1,000 people)
- confusion
- mood changes including anxiety
- taste changes
- tinnitus (ringing in the ears)
- inflammation of the liver (hepatitis) or your liver doesn’t work properly
- yellowing of the skin and eyes (jaundice).

Very rare side effects (probably affecting fewer than 1 in 10,000 people)
- excess sugar in the blood
- inflammation of the stomach
- vasculitis (inflammation of blood vessels, often with skin rash)
- certain blood disorders, which may increase the risk of bleeding, bruising or infections
- numbness in fingers or toes
- cough
- inflamed pancreas which causes severe pain in the abdomen and back
- allergic reactions (described above).

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE AMLODIPINE TABLETS

Keep out of the reach and sight of children

Store below 25°C.

Do not use Amlodipine Tablets after the expiry date, which is stated on the carton after EXP. The expiry date refers to the last day of that month.

Medicines should not be disposed via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Amlodipine Tablets contain:
- The active substance is amlodipine (as amlodipine besilate).
  Each tablet contains 5 mg or 10 mg of amlodipine.
- The other ingredients are calcium hydrogen phosphate dihydrate, microcrystalline cellulose, sodium starch glycolate and magnesium stearate.

What Amlodipine Tablets look like and the contents of the pack

Amlodipine 5 mg Tablets are white to off-white, elongated octagonal tablets, marked ‘AM5’ on one side and ‘-’ on the other side.

Amlodipine 10 mg Tablets are white to off-white, elongated octagonal tablets, marked ‘AM10’ on one side and ‘-’ on the other side.

Your medicine is available in blister packs containing 10, 20, 28, 30, 50, 56, 60, 98, 100 and 300 tablets (Amlodipine 5 mg Tablets) and 10, 20, 28, 30, 50, 60, 98 and 100 tablets (Amlodipine 10 mg Tablets). Not all pack sizes may be marketed.

Marketing Authorisation Holder:
Arrow Generics Limited, Unit 2, Eastman Way, Stevenage, Hertfordshire, SG1 4SZ

Manufacturer:
Arrow Pharm (Malta) Limited,
HF62, Hal Industrial Estate, Birkirkara BB906, Malta

This leaflet was last approved in (MM/YYYY)
Module 4
Labelling

5 mg:

Foil
10 mg:

Foil
Module 5
Scientific discussion during initial procedure

I. RECOMMENDATION
Based on the review of the data and the Applicant’s responses to questions raised by the RMS and CMSs on quality, safety and efficacy, the RMS considered that the applications for Amlodipine 5mg and 10mg Tablets in the treatment of essential hypertension and chronic stable and vasospastic anginal pectoris was approvable.

II. EXECUTIVE SUMMARY
II.1 Problem statement
Hypertension and ischaemic heart disease, including angina, remain major problems in the cardiovascular disease area. Pharmacotherapy remains the cornerstone of treatment. Calcium antagonists have been used for a long time for treatment of these conditions and have a good record of efficacy and safety through their extensive use in clinical practice.

II.2 About the product
Amlodipine besilate is a long-acting, dihydropyridine calcium channel-blocking agent with vascular selectivity. It inhibits the influx of calcium ions into cardiac and smooth muscle cells and differs from nifedipine by way of its slow onset of action and recovery. It is well established for use in the proposed indications.

II.3 General comments on the submitted dossier
The dossier is of good quality. The applicant submitted the overviews and summaries in CTD format and these were found to be helpful.

II.4 General comments on compliance with GMP, GLP, GCP and agreed ethical principles.
A current Certificate of GMP compliance for the finished product manufacturing site has been provided.

The bioequivalence study was conducted in compliance with GCP and in accordance with the Declaration of Helsinki and the US code of Federal Regulations.
III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

Drug substance
The applicant refers to the active substance manufacturer’s Certificate of Suitability.

The drug substance is a well known pharmaceutical active substance and its synthesis and control are satisfactory. The drug substance specification is in line with the Ph Eur monograph. Stability studies support the proposed retest interval.

It has been stated that the drug substance manufacturer has collaborated with the Pharmacopoeia regarding the revision of the amlodipine besilate monograph.

Drug Product
The finished products are formulated as immediate release tablets using conventional pharmaceutical ingredients. The development studies carried out were appropriate for these generic products. The manufacturing process is supported by pilot data and the applicant has committed to conduct further process validation studies in accordance with the protocol agreed in the dossier on consecutive production scale batches. The product specification includes relevant controls for a product of this nature. Stability studies of the final packaged product have been conducted appropriately in accordance with relevant guidelines and results support the proposed shelf-life (2 years) and label storage conditions (store below 25°C).

Summary of Product Characteristics (SmPCs), Patient Information Leaflet (PIL) and Labelling
The SmPCs, PIL and labelling are pharmaceutically acceptable. The UK approved PIL and label mock-ups are included in modules 3 and 4 of this report.

MAA forms
The MAA forms are pharmaceutically satisfactory.

Quality Overall Summary
The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Conclusion
From a quality point of view, it is recommended that Marketing Authorisations are granted for these applications.
III.2  Non-clinical aspects

**Pharmacology**
The pharmacology of amlodipine is well known. No new data have been submitted and none are required.

**Pharmacokinetics**
The pharmacokinetics of amlodpine are well known. No new data have been submitted and none are required.

**Toxicology**
The toxicological properties of amlodipine besilate are well known.

As amlodipine besilate is a widely used, well-known active substance, the applicant has not provided any new non-clinical data and none are required.

**Conclusion**
From a non-clinical point of view, it is recommended that Marketing Authorisations are granted for these applications.
III.3  Clinical aspects
The clinical pharmacology of amlodipine is well known.

Pharmacokinetics
The bioequivalence of Arrow’s Amlodipine 10 mg tablets to Istin 10 mg tablets was evaluated in a single dose, randomised, crossover, comparative study. The study was conducted in healthy male and female volunteers and complied with the Declaration of Helsinki, the US Code of Federal Regulations and GCP.

A total of 28 subjects were enrolled in the study, of which 25 completed. Out of the three withdrawals one was due to withdrawal of consent, one was due to an adverse reaction (hypersensitivity) and one for inappropriate concomitant medication administration. Subjects received study medication in a fasted state. The sampling period was 192 hours and the wash out period was at least 21 days.

Data from 24 subjects were analysed as per protocol.

<table>
<thead>
<tr>
<th>Summary pharmacokinetic data for amlodipine: mean (CV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parameter</td>
</tr>
<tr>
<td>Cmax (pg/ml)</td>
</tr>
<tr>
<td>AUC0-t (pg.hr/ml)</td>
</tr>
<tr>
<td>AUC0-∞ (pg.hr/ml)</td>
</tr>
<tr>
<td>tmax (hr)*</td>
</tr>
<tr>
<td>t½ (hr)</td>
</tr>
</tbody>
</table>

* tmax values are median  ** based on geometric LS means

Assessor’s comments on bioequivalence
When 25 subjects completed the study in its entirety, data from all 25 subjects should have been included in the final analysis. However, the confidence interval was narrow and exclusion of a single subject would not affect the data significantly. The protocol clearly defined the criteria for inclusion of the first 24 completers for analysis. Bioequivalence between the test product and Istin has been shown.

Pharmacodynamics
No new data have been submitted. The pharmacodynamics of amlodipine are well known.

Clinical efficacy
No new data have been submitted and none are required. The efficacy of amlodipine is well established from its extensive use in clinical practice.

Clinical safety
No new data have been submitted and none are required for this type of application. The safety profile of amlodipine is well known.
Summary of Product Characteristics (SmPCs), Patient Information Leaflet (PIL) and Labelling

The SmPCs, PIL and labelling are clinically satisfactory and consistent with those for the reference products, where appropriate.

MAA Forms

The MAA forms are clinically satisfactory.

Conclusions

The clinical efficacy and safety of amlodipine is well known from its extensive use in clinical practice. With the exception of the bioequivalence study, no new data were submitted and this is acceptable. Bioequivalence between the proposed product and Istin tablets has been shown. The benefit-risk ratio of the product is considered favourable.

From a clinical point of view, it is recommended that Marketing Authorisations are granted for these applications.
IV. OVERALL CONCLUSION AND BENEFIT RISK ASSESSMENT

QUALITY
The important quality characteristics of Amlodipine 5 mg and 10 mg Tablets are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit-risk balance.

NON-CLINICAL
The pharmacological and pharmacokinetic data submitted are satisfactory for an application of this type.

Results of the toxicology studies did not identify any properties likely to cause toxicity in humans when the product is used as directed in the SPC.

EFFICACY
Clinical studies have demonstrated the efficacy of Amlodipine 5 mg and 10 mg Tablets in the treatment of essential hypertension and chronic stable and vasospastic angina pectoris.

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with that for the innovator product.

BENEFIT-RISK ASSESSMENT
The quality of the products is acceptable and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with amlodipine besilate is considered to have demonstrated the therapeutic value of the compound. The benefit-risk ratio is, therefore, considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE – SUMMARY

Please note that the table below is not a complete list of variations approved since the grant of the product licences. Only type II and Ib, non-confidential, non-safety major clinical variations (granted since 01/04/2011) have been listed.

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>30/11/2011</td>
<td>Type IB Variation</td>
<td>To update the SmPC, to bring it in line with the Article 30 referral for “Norvasc and associated names”. (Commission Decision: C(2011)7283 published on 7.10.2011). Consequentially, the PIL has been updated.</td>
<td>Approved – 01/03/2012</td>
</tr>
</tbody>
</table>
Annex 1

Product Licence Numbers: PL 18909/0173-0030
PL 18909/0174-0028

European Procedure Numbers: UK/H/0862/001/IB/018
UK/H/0862/002/IB/018

Product: Amlodipine 5mg Tablets
Amlodipine 10mg Tablets

Marketing Authorisation Holder: Arrow Generics Limited

Active Ingredient(s): Amlodipine besilate

Reason:
To update the Summary of Product Characteristics (SmPC), to bring it in line with the Article 30 referral for “Norvasc and associated names”. (Commission Decision: C(2011)7283 published on 7.10.2011). Consequentially, the Patient Information leaflet (PIL) has been updated.

Supporting Evidence
In these Mutual Recognition (MR) Type II standard variation applications, the applicant has proposed changes to Sections 4.1 (Therapeutic indications), 4.2 (Posology and method of administration), 4.3 (Contraindications), 4.4 (Special warnings and precautions for use), 4.5 (Interaction with other medicinal products and other forms of interactions), 4.6 (Fertility, pregnancy and lactation), 4.7 (Effects on ability to drive and use machines), 4.8 (Undesirable effects), 4.9 (Overdose), 5.1 (Pharmacodynamic properties), 5.2 (Pharmacokinetic properties) and 5.3 (Preclinical safety data) of the SmPCs and the PIL.
The applicant has submitted:
- Existing and proposed SmPC
- Existing and proposed PIL

Evaluation
The proposed SmPC and PIL provided by the MAH are satisfactory.

THE FINAL APPROVED SMPC AND PIL ARE PRESENTED BELOW:

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Amlodipine 5mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 5mg of amlodipine (as amlodipine besilate)
For a full list of excipients see Section 6.1

3 PHARMACEUTICAL FORM
Tablet
White to off-white, elongated octagon-shaped tablets, embossed with ‘AM 5’ on one side and ‘>’ on the other side.

4 CLINICAL PARTICULARS
Therapeutic indications
Hypertension
Chronic stable angina pectoris
Vasospastic (Prinzmetal’s) angina

4.2 Posology and method of administration
Posology
Adults
For both hypertension and angina the usual initial dose is 5 mg Amlodipine once daily which may be
increased to a maximum dose of 10 mg depending on the individual patient's response.
In hypertensive patients, Amlodipine has been used in combination with a thiazide diuretic, alpha blocker,
beta blocker, or an angiotensin converting enzyme inhibitor. For angina, Amlodipine may be used as
monotherapy or in combination with other antianginal medicinal products in patients with angina that is
refractory to nitrates and/or to adequate doses of beta blockers.
No dose adjustment of Amlodipine is required upon concomitant administration of thiazide diuretics, beta
blockers, and angiotensin-converting enzyme inhibitors.

Special populations
Elderly
Amlodipine used at similar doses in elderly or younger patients is equally well tolerated. Normal dosage
regimens are recommended in the elderly, but increase of the dosage should take place with care (see
sections 4.4 and 5.2).

Hepatic impairment
Dosage recommendations have not been established in patients with mild to moderate hepatic impairment;
therefore dose selection should be cautious and should start at the lower end of the dosing range (see
sections 4.4 and 5.2). The pharmacokinetics of amlodipine have not been studied in severe hepatic
impairment. Amlodipine should be initiated at the lowest dose and titrated slowly in patients with severe
hepatic impairment.

Renal impairment
Changes in amlodipine plasma concentrations are not correlated with degree of renal impairment, therefore
the normal dosage is recommended. Amlodipine is not dialysable.

Paediatric population
Children and adolescents with hypertension from 6 years to 17 years of age
The recommended antihypertensive oral dose in paediatric patients ages 6-17 years is 2.5 mg once daily as
a starting dose, up-titrated to 5 mg once daily if blood pressure goal is not achieved after 4 weeks. Doses in
excess of 5 mg daily have not been studied in paediatric patients (see sections 5.1 and 5.2).
Doses of amlodipine 2.5 mg are not possible with this medicinal product.
Children under 6 years old
No data are available.

Method of administration
Tablet for oral administration.

4.3 Contraindications
Amlodipine is contra-indicated in patients with:
hypersensitivity to dihydropyridine derivatives, amlodipine or to any of the excipients.
severe hypotension
shock (including cardiogenic shock)
obstruction of the outflow tract of the left ventricle (e.g. high grade aortic stenosis)
haemodynamically unstable heart failure after acute myocardial infarction

4.4 Special warnings and precautions for use
The safety and efficacy of amlodipine in hypertensive crisis has not been established.

Patients with cardiac failure:
Patients with heart failure should be treated with caution. In a long-term, placebo controlled study in patients
with severe heart failure (NYHA grade III and IV) the reported incidence of pulmonary oedema was higher in
the amlodipine treated group than in the placebo group. (see Section 5.1)
Calcium channel blockers, including amlodipine, should be used with caution in patients with congestive heart failure, as they may increase the risk of future cardiovascular events and mortality.

*Use in patients with impaired hepatic function:* The half life of amlodipine is prolonged and AUC values are higher in patients with impaired liver function; dosage recommendations have not been established. Amlodipine should therefore be initiated at the lower end of the dosing range and caution should be used, both on initial treatment and when increasing the dose. Slow dose titration and careful monitoring may be required in patients with severe hepatic impairment.

*Use in elderly patients* In the elderly, increase of the dosage should take place with care (see Section 4.2 and 5.2).

*Use in renal failure:* Amlodipine may be used in such patients at normal doses. Changes in amlodipine plasma concentrations are not correlated with degree of renal impairment. Amlodipine is not dialyzable.

### 4.5 Interaction with other medicinal products and other forms of interactions

*Effects of other medicinal products on amlodipine*

**CYP3A4 inhibitors:** Concomitant use of amlodipine with strong or moderate CYP3A4 inhibitors (protease inhibitors, azole antifungals, macrolides like erythromycin or clarithromycin, verapamil or diltiazem) may give rise to significant increase in amlodipine exposure. The clinical translation of these PK variations may be more pronounced in the elderly. Clinical monitoring and dose adjustment may thus be required.

**CYP3A4 inducers:** There is no data available regarding the effect of CYP3A4 inducers on amlodipine. The concomitant use of CYP3A4 inducers (e.g., rifampicin, hypericum perforatum) may give a lower plasma concentration of amlodipine. Amlodipine should be used with caution together with CYP3A4 inducers.

Administration of amlodipine with grapefruit or grapefruit juice is not recommended as bioavailability may be increased in some patients resulting in increased blood pressure lowering effects.

**Dantrolene (infusion):** In animals, lethal ventricular fibrillation and cardiovascular collapse are observed in association with hyperkalemia after administration of verapamil and intravenous dantrolene. Due to risk of hyperkalemia, it is recommended that the co-administration of calcium channel blockers such as amlodipine be avoided in patients susceptible to malignant hyperthermia and in the management of malignant hyperthermia.

**Effects of amlodipine on other medicinal products**

The blood pressure lowering effects of amlodipine adds to the blood pressure-lowering effects of other medicinal products with antihypertensive properties.

In clinical interaction studies, amlodipine did not affect the pharmacokinetics of atorvastatin, digoxin, warfarin or cyclosporin.

### 4.6 Fertility, pregnancy and lactation

*Pregnancy*

The safety of amlodipine in human pregnancy has not been established.

In animal studies, reproductive toxicity was observed at high doses (see section 5.3).

Use in pregnancy is only recommended when there is no safer alternative and when the disease itself carries greater risk for the mother and foetus.

*Breast-feeding*

It is not known whether amlodipine is excreted in breast milk. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with amlodipine should be made taking into account the benefit of breast-feeding to the child and the benefit of amlodipine therapy to the mother.
Fertility
Reversible biochemical changes in the head of spermatozoa have been reported in some patients treated by calcium channel blockers. Clinical data are insufficient regarding the potential effect of amlodipine on fertility. In one rat study, adverse effects were found on male fertility (see section 5.3).

4.7 Effects on ability to drive and use machines
Amlodipine can have minor or moderate influence on the ability to drive and use machines. If patients taking amlodipine suffer from dizziness, headache, fatigue or nausea the ability to react may be impaired. Caution is recommended especially at the start of treatment.

4.8 Undesirable effects
Summary of the safety profile
The most commonly reported adverse reactions during treatment are somnolence, dizziness, headache, palpitations, flushing, abdominal pain, nausea, ankle swelling, oedema and fatigue.

Tabulated list of adverse reactions
The following adverse reactions have been observed and reported during treatment with amlodipine with the following frequencies: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to ≤1/100); rare (≥1/10,000 to ≤1/1,000); very rare (≤1/10,000).

<table>
<thead>
<tr>
<th>System organ class</th>
<th>Frequency</th>
<th>Undesirable effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and the lymphatic system disorder</td>
<td>Very rare</td>
<td>Leukocytopenia, thrombocytopenia</td>
</tr>
<tr>
<td>Immune system disorder</td>
<td>Very rare</td>
<td>Allergic reactions</td>
</tr>
<tr>
<td>Metabolism and nutrition disorder</td>
<td>Very rare</td>
<td>Hyperglycaemia</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Uncommon</td>
<td>Insomnia, mood changes (including anxiety), depression</td>
</tr>
<tr>
<td></td>
<td>Rare</td>
<td>Confusion</td>
</tr>
<tr>
<td>Nervous system disorder</td>
<td>Common</td>
<td>Somnolence, dizziness, headache (especially at the beginning of the treatment)</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Tremor, dysgeusia, syncope, hypoesthesia, paresthesia</td>
</tr>
<tr>
<td></td>
<td>Very rare</td>
<td>Hypertonia, peripheral neuropathy</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Uncommon</td>
<td>Visual disturbance (including diplopia)</td>
</tr>
<tr>
<td>Ear and labyrinth disorders</td>
<td>Uncommon</td>
<td>Tinnitus</td>
</tr>
<tr>
<td>Cardiac disorder</td>
<td>Common</td>
<td>Palpitations</td>
</tr>
<tr>
<td></td>
<td>Very rare</td>
<td>Myocardial infarction, arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation)</td>
</tr>
<tr>
<td>Vascular disorder</td>
<td>Common</td>
<td>Flushing</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Hypotension</td>
</tr>
<tr>
<td></td>
<td>Very rare</td>
<td>Vasculitis</td>
</tr>
<tr>
<td>Respiratory, thoracic and medicinal disorders</td>
<td>Uncommon</td>
<td>Dyspnoea, rhinitis</td>
</tr>
<tr>
<td></td>
<td>Very rare</td>
<td>Cough</td>
</tr>
<tr>
<td>Gastrointestinal disorder</td>
<td>Common</td>
<td>Abdominal pain, nausea</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Vomiting, dyspepsia, altered bowl habits (including diarrhea and constipation), dry mouth</td>
</tr>
<tr>
<td></td>
<td>Very rare</td>
<td>Pancreatitis, gastritis, gingival hyperplasia</td>
</tr>
<tr>
<td>Hepato-biliary disorders</td>
<td>Very rare</td>
<td>Hepatitis, jaundice, hepatic enzymes increased*</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Uncommon</td>
<td>Alopecia, purpura, skin discolouration, hyperhydrosis, pruritus, rash, exanthema</td>
</tr>
</tbody>
</table>
4.9 Overdose
In humans experience with intentional overdose is limited.

Symptoms:
Available data suggest that gross overdosage could result in excessive peripheral vasodilatation and possibly reflex tachycardia. Marked and probably prolonged systemic hypotension up to and including shock with fatal outcome have been reported.

Treatment:
Clinically significant hypotension due to amlodipine overdosage calls for active cardiovascular support including frequent monitoring of cardiac and respiratory function, elevation of extremities, and attention to circulating fluid volume and urine output.

A vasoconstrictor may be helpful in restoring vascular tone and blood pressure, provided that there is no contraindication to its use. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade.

Gastric lavage may be worthwhile in some cases. In healthy volunteers the use of charcoal up to 2 hours after administration of amlodipine 10mg has been shown to reduce the absorption rate of amlodipine.

Since amlodipine is highly protein-bound, dialysis is not likely to be of benefit.

5 PHARMACOLOGICAL PROPERTIES
Pharmacodynamic properties
Pharmacotherapeutic group: Calcium channel blockers, selective calcium channel blockers with mainly vascular effects. ATC Code: C08CA01.
Amlodipine is a calcium ion influx inhibitor of the dihydropyridine group (slow channel blocker or calcium ion antagonist) and inhibits the transmembrane influx of calcium ions into cardiac and vascular smooth muscle.

The mechanism of the antihypertensive action of amlodipine is due to a direct relaxant effect on vascular smooth muscle. The precise mechanism by which amlodipine relieves angina has not been fully determined but amlodipine reduces total ischaemic burden by the following two actions:

1) Amlodipine dilates peripheral arterioles and thus, reduces the total peripheral resistance (afterload) against which the heart works. Since the heart rate remains stable, this unloading of the heart reduces myocardial energy consumption and oxygen requirements.
2) The mechanism of action of amlodipine also probably involves dilatation of the main coronary arteries and coronary arterioles, both in normal and ischaemic regions. This dilatation increases myocardial oxygen delivery in patients with coronary artery spasm (Prinzmetal's or variant angina).

In patients with hypertension, once daily dosing provides clinically significant reductions of blood pressure in both the supine and standing positions throughout the 24 hour interval. Due to the slow onset of action, acute hypotension is not a feature of amlodipine administration.

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Use in patients with coronary artery disease (CAD)
The effectiveness of amlodipine in preventing clinical events in patients with coronary artery disease (CAD) has been evaluated in an independent, multi-center, randomized, double-blind, placebo controlled study of 1997 patients; Comparison of Amlodipine vs. Enalapril to Limit Occurrences of Thrombosis (CAMELOT). Of these patients, 663 were treated with amlodipine 5-10 mg, 673 patients were treated with enalapril 10-20 mg, and 655 patients were treated with placebo, in addition to standard care of statins, beta-blockers, diuretics and aspirin, for 2 years. The key efficacy results are presented in Table 1. The results indicate that amlodipine treatment was associated with fewer hospitalizations for angina and revascularization procedures in patients with CAD.

| Table 1. Incidence of significant clinical outcomes for CAMELOT |
|------------------|------------------|------------------|
| **Outcomes**     | **Cardiovascular event rates** | **Amlodipine vs. Placebo** |
|                  | **No. (%)** | **Amlodipine** | **Placebo** | **Enalapril** | **Hazard Ratio (95% CI)** | **P Value** |
| Primary Endpoint | 110 (16.6)   | 151 (23.1)     | 136 (20.2)  | 0.69 (0.54-0.88) | .003           |
| Adverse cardiovascular events | | | | | |
| Coronary revascularization | 78 (11.8)   | 103 (15.7)     | 95 (14.1)   | 0.73 (0.54-0.98) | .03            |
| Hospitalization for angina | 51 (7.7)    | 84 (12.8)      | 86 (12.8)   | 0.58 (0.41-0.82) | .002           |
| Nonfatal MI       | 14 (2.1)    | 19 (2.9)       | 11 (1.6)    | 0.73 (0.37-1.46) | .37            |
| Stroke or TIA     | 6 (0.9)     | 12 (1.8)       | 8 (1.2)     | 0.50 (0.19-1.32) | .15            |
| Cardiovascular death | 5 (0.8)   | 2 (0.3)        | 5 (0.7)     | 2.46 (0.48-12.7) | .27            |
| Hospitalization for CHF | 3 (0.5)   | 5 (0.8)        | 4 (0.6)     | 0.59 (0.14-2.47) | .46            |
| Resuscitated cardiac arrest | 0        | 4 (0.6)        | 1 (0.1)     | n/a             | .04            |
| New-onset peripheral vascular disease | 5 (0.8)   | 2 (0.3)        | 8 (1.2)     | 2.6 (0.50-13.4)  | .24            |

Abbreviations: CHF, congestive heart failure; CI, confidence interval; MI, myocardial infarction; TIA, transient ischemic attack.

Use in patients with heart failure
Haemodynamic studies and exercise based controlled clinical trials in NYHA Class II-IV heart failure patients have shown that amlodipine did not lead to clinical deterioration as measured by exercise tolerance, left ventricular ejection fraction and clinical symptomatology.

A placebo controlled study (PRAISE) designed to evaluate patients in NYHA Class III-IV heart failure receiving digoxin, diuretics and ACE inhibitors has shown that amlodipine did not lead to an increase in risk of mortality or combined mortality and morbidity with heart failure.

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disease, on stable doses of ACE inhibitors, digitalis, and diuretics, amlodipine had no effect on total cardiovascular mortality. In this same population amlodipine was associated with increased reports of pulmonary oedema.

**Treatment to prevent heart attack trial (ALLHAT)**
A randomized double-blind morbidity-mortality study called the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) was performed to compare newer drug therapies: amlodipine 2.5-10 mg/d (calcium channel blocker) or lisinopril 10-40 mg/d (ACE-inhibitor) as first-line therapies to that of the thiazide-diuretic, chlorthalidone 12.5-25 mg/d in mild to moderate hypertension.”

A total of 33,357 hypertensive patients aged 55 or older were randomized and followed for a mean of 4.9 years. The patients had at least one additional CHD risk factor, including: previous myocardial infarction or stroke (> 6 months prior to enrollment) or documentation of other atherosclerotic CVD (overall 51.5%), type 2 diabetes (36.1%), HDL-C < 35 mg/dL (11.6%), left ventricular hypertrophy diagnosed by electrocardiogram or echocardiography (20.9%), current cigarette smoking (21.9%).

The primary endpoint was a composite of fatal CHD or non-fatal myocardial infarction. There was no significant difference in the primary endpoint between amlodipine-based therapy and chlorthalidone-based therapy: RR 0.98 95% CI (0.90-1.07) p=0.65. Among secondary endpoints, the incidence of heart failure (component of a composite combined cardiovascular endpoint) was significantly higher in the amlodipine group as compared to the chlorthalidone group (10.2% vs. 7.7%, RR 1.38, 95% CI [1.25-1.52] p<0.001). However, there was no significant difference in all-cause mortality between amlodipine-based therapy and chlorthalidone-based therapy. RR 0.96 95% CI [0.89-1.02] p=0.20.

**Use in children (aged 6 years and older)**
In a study involving 268 children aged 6-17 years with predominantly secondary hypertension, comparison of a 2.5mg dose, and 5.0 mg dose of amlodipine with placebo, showed that both doses reduced Systolic Blood Pressure significantly more than placebo. The difference between the two doses was not statistically significant.

The long-term effects of amlodipine on growth, puberty and general development have not been studied. The long-term efficacy of amlodipine on therapy in childhood to reduce cardiovascular morbidity and mortality in adulthood have also not been established.

**5.2 Pharmacokinetic properties**
**Absorption, distribution, plasma protein binding:** After oral administration of therapeutic doses, amlodipine is well absorbed with peak blood levels between 6-12 hours post dose. Absolute bioavailability has been estimated to be between 64 and 80%. The volume of distribution is approximately 21 l/kg. In vitro studies have shown that approximately 97.5% of circulating amlodipine is bound to plasma proteins. The bioavailability of amlodipine is not affected by food intake.

**Biotransformation/elimination**
The terminal plasma elimination half life is about 35-50 hours and is consistent with once daily dosing. Amlodipine is extensively metabolised by the liver to inactive metabolites with 10% of the parent compound and 60% of metabolites excreted in the urine.

**Use in hepatic impairment**
Very limited clinical data are available regarding amlodipine administration in patients with hepatic impairment. Patients with hepatic insufficiency have decreased clearance of amlodipine resulting in a longer half-life and an increase in AUC of approximately 40-60%.

**Use in the elderly**
The time to reach peak plasma concentrations of amlodipine is similar in elderly and younger subjects. Amlodipine clearance tends to be decreased with resulting increases in AUC and elimination half-life in elderly patients. Increases in AUC and elimination half-life in patients with congestive heart failure were as expected for the patient age group studied.
Use in children
A population PK study has been conducted in 74 hypertensive children aged from 1 to 17 years (with 34 patients aged 6 to 12 years and 28 patients aged 13 to 17 years) receiving amlodipine between 1.25 and 20 mg given either once or twice daily. In children 6 to 12 years and in adolescents 13-17 years of age the typical oral clearance (CL/F) was 22.5 and 27.4 L/hr respectively in males and 16.4 and 21.3 L/hr respectively in females. Large variability in exposure between individuals was observed. Data reported in children below 6 years is limited.

5.3 Preclinical safety data
Reproductive toxicology
Reproductive studies in rats and mice have shown delayed date of delivery, prolonged duration of labour and decreased pup survival at dosages approximately 50 times greater than the maximum recommended dosage for humans based on mg/kg.

Impairment of fertility
There was no effect on the fertility of rats treated with amlodipine (males for 64 days and females 14 days prior to mating) at doses up to 10 mg/kg/day (8 times* the maximum recommended human dose of 10 mg on a mg/m² basis). In another rat study in which male rats were treated with amlodipine besilate for 30 days at a dose comparable with the human dose based on mg/kg, decreased plasma follicle-stimulating hormone and testosterone were found as well as decreases in sperm density and in the number of mature spermatids and Sertoli cells.

Carcinogenesis, mutagenesis
Rats and mice treated with amlodipine in the diet for two years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 mg/kg/day showed no evidence of carcinogenicity. The highest dose (for mice, similar to, and for rats twice* the maximum recommended clinical dose of 10 mg on a mg/m² basis) was close to the maximum tolerated dose for mice but not for rats. Mutagenicity studies revealed no drug related effects at either the gene or chromosome levels.

*Based on patient weight of 50 kg

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Calcium hydrogen phosphate dihydrate
Microcrystalline cellulose
Sodium starch glycolate (type A)
Magnesium stearate

6.2 Incompatibilities
Not applicable

6.3 Shelf life
3 years

6.4 Special precautions for storage
Store below 25°C

6.5 Nature and contents of container
PVC/Aclar/Aluminium Foil Blister Packs.
* Pack sizes 10, 20, 28, 30, 50, 56, 60, 98, 100, 300 tablets.
* Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements

7 MARKETING AUTHORISATION HOLDER
Arrow Generics Limited
Unit 2, Eastman Way
Stevenage
Hertfordshire
SG1 4SZ
United Kingdom

8 MARKETING AUTHORIZATION NUMBER
PL 18909/0173

9 DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION
07/03/2007

10 DATE OF REVISION OF THE TEXT
01/03/2012
1 NAME OF THE MEDICINAL PRODUCT
Amlodipine 10mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 10mg of amlodipine (as amlodipine besilate)
For a full list of excipients see Section 6.1

3 PHARMACEUTICAL FORM
Tablet
White to off-white, elongated octagon-shaped tablets, embossed with ‘AM 10’ on one side and ‘>’ on the other side.

4 CLINICAL PARTICULARS
4.2 Posology and method of administration
Posology
Adults
For both hypertension and angina the usual initial dose is 5 mg Amlodipine once daily which may be increased to a maximum dose of 10 mg depending on the individual patient's response.
In hypertensive patients, Amlodipine has been used in combination with a thiazide diuretic, alpha blocker, beta blocker, or an angiotensin converting enzyme inhibitor. For angina, Amlodipine may be used as monotherapy or in combination with other antianginal medicinal products in patients with angina that is refractory to nitrates and/or to adequate doses of beta blockers.
No dose adjustment of Amlodipine is required upon concomitant administration of thiazide diuretics, beta blockers, and angiotensin-converting enzyme inhibitors.

Special populations
Elderly
Amlodipine used at similar doses in elderly or younger patients is equally well tolerated. Normal dosage regimens are recommended in the elderly, but increase of the dosage should take place with care (see sections 4.4 and 5.2).

Hepatic impairment
Dosage recommendations have not been established in patients with mild to moderate hepatic impairment; therefore dose selection should be cautious and should start at the lower end of the dosing range (see sections 4.4 and 5.2). The pharmacokinetics of amlodipine have not been studied in severe hepatic impairment. Amlodipine should be initiated at the lowest dose and titrated slowly in patients with severe hepatic impairment.

Renal impairment
Changes in amlodipine plasma concentrations are not correlated with degree of renal impairment, therefore the normal dosage is recommended. Amlodipine is not dialysable.

Paediatric population
Children and adolescents with hypertension from 6 years to 17 years of age
The recommended antihypertensive oral dose in paediatric patients ages 6-17 years is 2.5 mg once daily as a starting dose, up-titrated to 5 mg once daily if blood pressure goal is not achieved after 4 weeks. Doses in excess of 5 mg daily have not been studied in paediatric patients (see sections 5.1 and 5.2).
Doses of amlodipine 2.5 mg are not possible with this medicinal product.
Children under 6 years old
No data are available.

Method of administration
Tablet for oral administration.
4.3 **Contraindications**
Amlodipine is contra-indicated in patients with:
- hypersensitivity to dihydropyridine derivatives, amlodipine or to any of the excipients.
- severe hypotension
- shock (including cardiogenic shock)
- obstruction of the outflow tract of the left ventricle (e.g. high grade aortic stenosis)
- haemodynamically unstable heart failure after acute myocardial infarction

4.4 **Special warnings and precautions for use**
The safety and efficacy of amlodipine in hypertensive crisis has not been established.

*Patients with cardiac failure:*
Patients with heart failure should be treated with caution. In a long-term, placebo controlled study in patients with severe heart failure (NYHA grade III and IV) the reported incidence of pulmonary oedema was higher in the amlodipine treated group than in the placebo group. (see Section 5.1)

*Use in patients with impaired hepatic function:*
The half life of amlodipine is prolonged and AUC values are higher in patients with impaired liver function; dosage recommendations have not been established. Amlodipine should therefore be initiated at the lower end of the dosing range and caution should be used, both on initial treatment and when increasing the dose. Slow dose titration and careful monitoring may be required in patients with severe hepatic impairment.

*Use in elderly patients*
In the elderly, increase of the dosage should take place with care (see Section 4.2 and 5.2).

*Use in renal failure:*
Amlodipine may be used in such patients at normal doses. Changes in amlodipine plasma concentrations are not correlated with degree of renal impairment. Amlodipine is not dialyzable.

4.5 **Interaction with other medicinal products and other forms of interactions**

*Effects of other medicinal products on amlodipine*
CYP3A4 inhibitors: Concomitant use of amlodipine with strong or moderate CYP3A4 inhibitors (protease inhibitors,azole antifungals, macrolides like erythromycin or clarithromycin, verapamil or diltiazem) may give rise to significant increase in amlodipine exposure. The clinical translation of these PK variations may be more pronounced in the elderly. Clinical monitoring and dose adjustment may thus be required.

CYP3A4 inducers: There is no data available regarding the effect of CYP3A4 inducers on amlodipine. The concomitant use of CYP3A4 inducers (e.g., rifampicin, hypericum perforatum) may give a lower plasma concentration of amlodipine. Amlodipine should be used with caution together with CYP3A4 inducers.

Administration of amlodipine with grapefruit or grapefruit juice is not recommended as bioavailability may be increased in some patients resulting in increased blood pressure lowering effects.

Dantrolene (infusion): In animals, lethal ventricular fibrillation and cardiovascular collapse are observed in association with hyperkalemia after administration of verapamil and intravenous dantrolene. Due to risk of hyperkalemia, it is recommended that the co-administration of calcium channel blockers such as amlodipine be avoided in patients susceptible to malignant hyperthermia and in the management of malignant hyperthermia.

Effects of amlodipine on other medicinal products
The blood pressure lowering effects of amlodipine adds to the blood pressure-lowering effects of other medicinal products with antihypertensive properties.
In clinical interaction studies, amlodipine did not affect the pharmacokinetics of atorvastatin, digoxin, warfarin or cyclosporin.

4.6 **Fertility, pregnancy and lactation**

*Pregnancy*
The safety of amlodipine in human pregnancy has not been established.
In animal studies, reproductive toxicity was observed at high doses (see section 5.3).
Use in pregnancy is only recommended when there is no safer alternative and when the disease itself carries greater risk for the mother and foetus.

Breast-feeding
It is not known whether amlodipine is excreted in breast milk. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with amlodipine should be made taking into account the benefit of breast-feeding to the child and the benefit of amlodipine therapy to the mother.

Fertility
Reversible biochemical changes in the head of spermatozoa have been reported in some patients treated by calcium channel blockers. Clinical data are insufficient regarding the potential effect of amlodipine on fertility. In one rat study, adverse effects were found on male fertility (see section 5.3).

4.7 Effects on ability to drive and use machines
Amlodipine can have minor or moderate influence on the ability to drive and use machines. If patients taking amlodipine suffer from dizziness, headache, fatigue or nausea the ability to react may be impaired. Caution is recommended especially at the start of treatment.

4.8 Undesirable effects
Summary of the safety profile
The most commonly reported adverse reactions during treatment are somnolence, dizziness, headache, palpitations, flushing, abdominal pain, nausea, ankle swelling, oedema and fatigue.

Tabulated list of adverse reactions
The following adverse reactions have been observed and reported during treatment with amlodipine with the following frequencies: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to ≤1/100); rare (≥1/10,000 to ≤1/1,000); very rare (≤1/10,000).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

<table>
<thead>
<tr>
<th>System organ class</th>
<th>Frequency</th>
<th>Undesirable effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and the lymphatic system disorder</td>
<td>Very rare</td>
<td>Leukocytopenia, thrombocytopenia</td>
</tr>
<tr>
<td>Immune system disorder</td>
<td>Very rare</td>
<td>Allergic reactions</td>
</tr>
<tr>
<td>Metabolism and nutrition disorder</td>
<td>Very rare</td>
<td>Hyperglycaemia</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Uncommon</td>
<td>Insomnia, mood changes (including anxiety), depression</td>
</tr>
<tr>
<td></td>
<td>Rare</td>
<td>Confusion</td>
</tr>
<tr>
<td>Nervous system disorder</td>
<td>Common</td>
<td>Somnolence, dizziness, headache (especially at the beginning of the treatment)</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Tremor, dysgeusia, syncope, hypoesthesia, paresthesia</td>
</tr>
<tr>
<td></td>
<td>Very rare</td>
<td>Hypertonia, peripheral neuropathy</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Uncommon</td>
<td>Visual disturbance (including diplopia)</td>
</tr>
<tr>
<td>Ear and labyrinth disorders</td>
<td>Uncommon</td>
<td>Tinnitus</td>
</tr>
<tr>
<td>Cardiac disorder</td>
<td>Common</td>
<td>Palpitations</td>
</tr>
<tr>
<td></td>
<td>Very rare</td>
<td>Myocardial infarction, arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation)</td>
</tr>
<tr>
<td>Vascular disorder</td>
<td>Common</td>
<td>Flushing</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Hypotension</td>
</tr>
<tr>
<td></td>
<td>Very rare</td>
<td>Vasculitis</td>
</tr>
<tr>
<td>Respiratory, thoracic and medicinal disorders</td>
<td>Uncommon</td>
<td>Dyspnoea, rhinitis</td>
</tr>
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<td></td>
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<tr>
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<tr>
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</tr>
<tr>
<td>Adverse cardiovascular events</td>
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<tr>
<td>Individual Components:</td>
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<tr>
<td>Coronary revascularization</td>
</tr>
<tr>
<td>Hospitalization for angina</td>
</tr>
<tr>
<td>Nonfatal MI</td>
</tr>
<tr>
<td>Stroke or TIA</td>
</tr>
<tr>
<td>Cardiovascular death</td>
</tr>
<tr>
<td>Hospitalization for CHF</td>
</tr>
<tr>
<td>Resuscitated cardiac arrest</td>
</tr>
<tr>
<td>New-onset peripheral vascular disease</td>
</tr>
</tbody>
</table>

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Treatment to prevent heart attack trial (ALLHAT)
A randomized double-blind morbidity-mortality study called the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) was performed to compare newer drug therapies: amlodipine 2.5-10 mg/d (calcium channel blocker) or lisinopril 10-40 mg/d (ACE-inhibitor) as first-line therapies to that of the thiazide-diuretic, chlorthalidone 12.5-25 mg/d in mild to moderate hypertension.” A total of 33,357 hypertensive patients aged 55 or older were randomized and followed for a mean of 4.9 years. The patients had at least one additional CHD risk factor, including: previous myocardial infarction or stroke (> 6 months prior to enrollment) or documentation of other atherosclerotic CVD (overall 51.5%), type 2 diabetes (36.1%), HDL-C < 35 mg/dL (11.6%), left ventricular hypertrophy diagnosed by electrocardiogram or echocardiography (20.9%), current cigarette smoking (21.9%).

The primary endpoint was a composite of fatal CHD or non-fatal myocardial infarction. There was no significant difference in the primary endpoint between amlodipine-based therapy and chlorthalidone-based therapy: RR 0.98 95% CI (0.90-1.07) p=0.65. Among secondary endpoints, the incidence of heart failure (component of a composite combined cardiovascular endpoint) was significantly higher in the amlodipine group as compared to the chlorthalidone group (10.2% vs. 7.7%, RR 1.38, 95% CI [1.25-1.52] p<0.001). However, there was no significant difference in all-cause mortality between amlodipine-based therapy and chlorthalidone-based therapy. RR 0.96 95% CI [0.89-1.02] p=0.20.

Use in children (aged 6 years and older)
In a study involving 268 children aged 6-17 years with predominantly secondary hypertension, comparison of a 2.5mg dose, and 5.0 mg dose of amlodipine with placebo, showed that both doses reduced Systolic Blood Pressure significantly more than placebo. The difference between the two doses was not statistically significant.

The long-term effects of amlodipine on growth, puberty and general development have not been studied. The long-term efficacy of amlodipine on therapy in childhood to reduce cardiovascular morbidity and mortality in adulthood have also not been established.

5.2 Pharmacokinetic properties
Absorption, distribution, plasma protein binding: After oral administration of therapeutic doses, amlodipine is well absorbed with peak blood levels between 6-12 hours post dose. Absolute bioavailability has been estimated to be between 64 and 80%. The volume of distribution is approximately 21 l/kg. In vitro studies have shown that approximately 97.5% of circulating amlodipine is bound to plasma proteins.

The bioavailability of amlodipine is not affected by food intake.

Biotransformation/elimination
The terminal plasma elimination half life is about 35-50 hours and is consistent with once daily dosing. Amlodipine is extensively metabolised by the liver to inactive metabolites with 10% of the parent compound and 60% of metabolites excreted in the urine.

Use in hepatic impairment
Very limited clinical data are available regarding amlodipine administration in patients with hepatic impairment. Patients with hepatic insufficiency have decreased clearance of amlodipine resulting in a longer half-life and an increase in AUC of approximately 40-60%.

Use in the elderly
The time to reach peak plasma concentrations of amlodipine is similar in elderly and younger subjects. Amlodipine clearance tends to be decreased with resulting increases in AUC and elimination half-life in
elderly patients. Increases in AUC and elimination half-life in patients with congestive heart failure were as expected for the patient age group studied.

Use in children
A population PK study has been conducted in 74 hypertensive children aged from 1 to 17 years (with 34 patients aged 6 to 12 years and 28 patients aged 13 to 17 years) receiving amlodipine between 1.25 and 20 mg given either once or twice daily. In children 6 to 12 years and in adolescents 13-17 years of age the typical oral clearance (CL/F) was 22.5 and 27.4 L/hr respectively in males and 16.4 and 21.3 L/hr respectively in females. Large variability in exposure between individuals was observed. Data reported in children below 6 years is limited.

5.3 Preclinical safety data
Reproductive toxicology
Reproductive studies in rats and mice have shown delayed date of delivery, prolonged duration of labour and decreased pup survival at dosages approximately 50 times greater than the maximum recommended dosage for humans based on mg/kg.

Impairment of fertility
There was no effect on the fertility of rats treated with amlodipine (males for 64 days and females 14 days prior to mating) at doses up to 10 mg/kg/day (8 times* the maximum recommended human dose of 10 mg on a mg/m² basis). In another rat study in which male rats were treated with amlodipine besilate for 30 days at a dose comparable with the human dose based on mg/kg, decreased plasma follicle-stimulating hormone and testosterone were found as well as decreases in sperm density and in the number of mature spermatids and Sertoli cells.

Carcinogenesis, mutagenesis
Rats and mice treated with amlodipine in the diet for two years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 mg/kg/day showed no evidence of carcinogenicity. The highest dose (for mice, similar to, and for rats twice* the maximum recommended clinical dose of 10 mg on a mg/m² basis) was close to the maximum tolerated dose for mice but not for rats. Mutagenicity studies revealed no drug related effects at either the gene or chromosome levels.

*Based on patient weight of 50 kg

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Calcium hydrogen phosphate dihydrate
Microcrystalline cellulose
Sodium starch glycolate (type A)
Magnesium stearate

6.2 Incompatibilities
Not applicable

6.3 Shelf life
3 years

6.4 Special precautions for storage
Store below 25°C

6.5 Nature and contents of container
PVC/Aclar/Aluminium Foil Blister Packs.
* Pack sizes 10, 14, 20, 28, 30, 50, 56, 60, 98, 100 tablets.
* Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements

7 MARKETING AUTHORIZATION HOLDER
Arrow Generics Limited
Unit 2, Eastman Way
PAR Amlodipine 5 mg and 10 mg Tablets

Stevenage
Hertfordshire
SG1 4SZ
United Kingdom

8 MARKETING AUTHORISATION NUMBER
PL 18909/0174

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
07/03/2007

10 DATE OF REVISION OF THE TEXT
01/03/2012
PAR Amlodipine 5 mg and 10 mg Tablets

UK/H/0862/001-2/DC

PATIENT INFORMATION LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER
Amlodipine 5 mg and 10 mg Tablets
(Amlodipine besilate)

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Amlodipine Tablets are and what they are used for
2. Before you take Amlodipine Tablets
3. How to take Amlodipine Tablets
4. Possible side effects
5. How to store Amlodipine Tablets
6. Further information

1. WHAT AMLODIPINE TABLETS ARE AND WHAT THEY ARE USED FOR
Amlodipine Tablets contain the active substance amlodipine which belongs to a group of medicines called calcium antagonists. Amlodipine Tablets are used to treat high blood pressure (hypertension) or a certain type of chest pain called angina, a rare form of which is Prinzmetal’s or variant angina.
In patients with high blood pressure your medicine works by relaxing blood vessels, so that blood passes through them more easily. In patients with angina Amlodipine Tablets works by improving blood supply to the heart muscle which then receives more oxygen and as a result chest pain is prevented. Your medicine does not provide immediate relief of chest pain from angina.

2. BEFORE YOU TAKE AMLODIPINE TABLETS
Do not take Amlodipine Tablets
- If you are allergic (hypersensitive) to amlodipine, or any of the other ingredients of your medicine listed in section 6, or to any other calcium antagonists. This may be itching, reddening of the skin or difficulty in breathing.
- If you have severe low blood pressure (hypotension)
- If you have narrowing of the aortic heart valve (aortic stenosis) or cardiogenic shock (a condition where your heart is unable to supply enough blood to the body).
- If you suffer from heart failure after a heart attack

Take special care with Amlodipine Tablets
You should inform your doctor if you have or have had any of the following conditions:
- Recent heart attack
- Heart failure
- Severe increase in blood pressure (hypertensive crisis)
- Liver disease
- You are elderly and your dose needs to be increased

Use in children and adolescents
Amlodipine Tablets has not been studied in children under the age of 6 years. Amlodipine Tablets should only be used for hypertension in children and adolescents from 6 years to 17 years of age (see section 4).
For more information, talk to your doctor.

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.
Amlodipine Tablets may affect or be affected by other medicines, such as:
- ketoconazole, itraconazole (anti-fungal medicines)
- ritonavir, indinavir, nevirapin (so called protease inhibitors used to treat HIV)
- rifampicin, erythromycin, clarithromycin (antibiotics)
- hypericum perforatum (St John’s Wort)
- warfarin, diltiazem (heart medicines)
- dantronine (infusion for severe body temperature abnormalities).
Amlodipine tablets may lower your blood pressure even more if you are already taking other medicines to treat your high blood pressure.

Taking Amlodipine Tablets with food and drink
Grapefruit juice and grapefruit should not be consumed by people who are taking Amlodipine Tablets. This is because grapefruit and grapefruit juice can lead to an increase in the blood levels of the active ingredient amlodipine, which can cause an unpredictable increase in the blood pressure lowering effect of Amlodipine Tablets.

Pregnancy
The safety of amlodipine in human pregnancy has not been established. If you think you might be pregnant, or are planning to get pregnant, you must tell your doctor before you take Amlodipine Tablets.

Breast-feeding
It is not known whether amlodipine is passed into breast milk. If you are breast-feeding or about to start breast-feeding you must tell your doctor before taking Amlodipine Tablets. Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
Amlodipine Tablets may affect your ability to drive or use machines. If the tablets make you feel sick, dizzy or tired, or give you a headache, do not drive or use machines and contact your doctor immediately.

Important information about some of the ingredients of Amlodipine Tablets
This medicine contains less than 1 mmol sodium (23 mg) per tablet which means is essentially ‘sodium-free’.

3. HOW TO TAKE AMLODIPINE TABLETS
Always take your medicine exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.
The usual initial dose is Amlodipine Tablets 5 mg once daily.
The dose can be increased to Amlodipine Tablets 10 mg once daily.
Your medicine can be used before or after food and drinks.
You should take your medicine at the same time each day with a drink of water. Do not take Amlodipine Tablets with grapefruit juice.

Use in children and adolescents
For children and adolescents (6-17 years old), the recommended usual starting dose is 2.5 mg a day. The maximum recommended dose is 5 mg a day. Amlodipine 2.5 mg is not currently available and the 2.5 mg dose cannot be obtained with Amlodipine Tablets 5 mg tablets as these tablets are not manufactured to break into two equal halves.
It is important to keep taking the tablets. Do not wait until your tablets are finished before seeing your doctor.
If you take more Amlodipine Tablets than you should
Taking too many tablets may cause your blood pressure to become low or even dangerously low. You may feel dizzy, lightheaded, faint or weak. If blood pressure drop is severe enough shock can occur.
Your skin could feel cool and clammy and you could lose consciousness. Seek immediate medical attention if you take too many Amlodipine tablets.
PAR Amlodipine 5 mg and 10 mg Tablets

If you forget to take Amlodipine Tablets
Do not worry. If you forget to take a tablet, leave out that dose completely. Take your next dose at the right time. Do not take a double dose to make up for a missed dose.

If you stop taking Amlodipine Tablets
Your doctor will advise you how long to take your medicine. Your condition may return if you stop using your medicine before you are advised.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Amlodipine Tablets can cause side effects, although not everyone gets them.

Visit your doctor immediately if you experience any of the following very rare, severe side effects after taking this medicine.
- Sudden wheeziness, chest pain, shortness of breath or difficulty in breathing
- Swelling of eyelids, face or lips
- Swelling of the tongue and throat which causes great difficulty in breathing
- Severe skin reactions including intense skin rash, hives, reddening of the skin over your whole body, severe itching, blistering, peeling and swelling of the skin, inflammation of mucous membranes (Stevens Johnson Syndrome) or other allergic reactions
- Heart attack, abnormal heart beat
- Inflamed pancreas which may cause severe abdominal and back pain accompanied with feeling very unwell.

The following common side-effects have been reported. If any of these occur you problems or if they last for more than one week, you should contact your doctor.

Common: affects 1 to 10 users in 100
- Headache, dizziness, sleeplessness (especially at the beginning of treatment)
- Palpitations (awareness of your heart beat), flushing
- Abdominal pain, feeling sick (nausea)
- Ankle swelling (oedema), tiredness.

Other side-effects that have been reported include the following list. If any of these get serious, or if you notice any side-effects not listed in this leaflet, please tell your doctor or pharmacist.

Uncommon: affects 1 to 10 users in 1,000
- Mood changes, anxiety, depression, sleeplessness
- Trembling, taste abnormalities, fainting, weakness
- Numbness or tingling sensation in your limbs; loss of pain sensation
- Visual disturbances, double vision, ringing in the ears
- Low blood pressure
- Sneezing/running nose caused by inflammation of the lining of the nose (rhinitis)
- Altered bowel habits, diarrhoea, constipation, indigestion, dry mouth, vomiting (being sick)
- Hair loss, increased sweating, itchy skin, red patches on skin, skin discolouration
- Disorder in passing urine, increased need to urinate at night, increased number of times of passing urine
- Inability to obtain an erection; discomfort or enlargement of the breasts in men
- Weakness, pain, feeling unwell
- Joint or muscle pain, muscle cramps, back pain
- Weight increase or decrease.

Rare: affects 1 to 10 users in 10,000
- Confusion.

Very rare: affects less than 1 user in 10,000
- Decreased numbers of white blood cells, decrease in blood platelets which may result in unusual bruising or easy bleeding (red blood cell damage)
- Excess sugar in blood (hyperglycaemia)
- A disorder of the nerves which can cause weakness, tingling or numbness
- Cough, swelling of the gums
- Abdominal bloating (gastro) 
- Abnormal liver function, inflammation of the liver (hepatitis), yellowing of the skin (jaundice), liver enzyme increase which may have an effect on some medical tests
- Increased muscle tension
- Inflammation of blood vessels, often with skin rash
- Sensitivity to light
- Disorders combining rigidity, tremor, and/or movement disorders.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE AMLODIPINE TABLETS

Keep out of the reach of children

Do not use Amlodipine Tablets after the expiry date, which is stated on the carton after “EXP”. The expiry date refers to the last day of that month.

Tablets

Do not store above 25°C.

Medicines should not be disposed via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Amlodipine Tablets contain:
- The active substance is amlodipine (as amlodipine besilate). Each tablet contains 5 mg or 10 mg of amlodipine.
- The other ingredients are calcium hydrogen phosphate dihydrate, microcrystalline cellulose, sodium starch glycolate and magnesium stearate.

What Amlodipine Tablets look like and the contents of the pack
Amlodipine 5 mg Tablets are white to off-white, elongated octagonal tablets, marked “AMS” on one side and “>” on the other side.
Amlodipine 10 mg Tablets are white to off-white, elongated octagonal tablets, marked “AM10” on one side and “>” on the other side.
Your medicine is available in blisters containing 10, 20, 28, 30, 50, 56, 60, 98, 100 and 300 tablets Amlodipine 5 mg Tablets and 10, 14, 20, 28, 30, 50, 60, 90, 98 and 100 tablets Amlodipine 10 mg Tablets. Not all pack sizes may be marketed.

Marketing Authorisation Holder:
Arrow Generics Limited, Unit 2, Eastman Way, Stevenage, Hertfordshire, SG1 4SZ.

Manufacturer:
Arrow Pharm (Malta) Limited,
HF62, Hal Industrial Estate, Birżebbuġa BBG06, Malta.

This leaflet was last approved in 02/2012.
Conclusion
The proposed SmPC and PIL changes are therefore acceptable.

Decision – Granted 01/03/2012